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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,872	10/22/2003	Jane Hirsh	73690.000120	6830

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,872	HIRSH ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-12,14-17,19-21 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12,14-17,19-21 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/22/08 has been entered.

Status of Claims

Claims 1-3, 6-9, 15-17 and 19 have been amended. Claims 4, 5, 13, 18 and 22-24 have been cancelled. Claims 25-28 are newly added. Claims 1-3, 6-12, 14-17, 19-21 and 25-28 are pending and are examined herein on the merits for patentability

Response to Arguments

Any rejections not reiterated herein have been withdrawn.

Applicant's arguments with respect to claims 1-4, 6-10, 15-17 and 19-22 under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137), have been considered but are not found to be persuasive for reasons set forth hereinbelow.

Applicant's arguments with respect to claims 1-12, 15-17 and 19-22 under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137), further in view of Pailard (US 6,699,506) have been considered but are not found to be persuasive for reasons set forth hereinbelow.

Declaration under 37 CFR 1.132

The declaration under 37 CFR 1.132 filed 1/3/2008 is insufficient to overcome the rejection of claims the pending claims based upon the Midha and Ansseau references as set forth in the last Office action because: It refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-12, 14-17, 19-21 and 25-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 11/192,697. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to "a milnacipran formulation that provides pulsatile release of milnacipran wherein the formulation comprises (a) an immediate release dosage unit... (b) a first delayed release dosage unit... and optionally (c) a second delayed release dosage unit," and those of the '697 Application are drawn to "a method of making a milnacipran formulation comprising providing a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished side effects or reduced intensity relative to one or more immediate release milnacipran side effects," and the claims include providing components a-c (e.g. see claim 31). It would have been obvious to one of ordinary skill in the art at the time of the instant invention to "provide" and "administer" a milnacipran formulation having the properties of the formulation of the instant application, and thus to accomplish the claimed methods of making and delivering a therapeutic dose of milnacipran, as in the '697 Application, because it is

well-known in the art that the purpose of any given pharmaceutical agent is for administration to a patient.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-12, 14-17, 19-21 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a milnacipran formulation that provides pulsatile release of milnacipran wherein the formulation comprises: (a) an immediate release dosage unit comprising a first dose of milnacipran that is released substantially immediately following oral administration of the formulation to a patient resulting in a first plasma level peak at a time between approximately 0.05 hours to less than 3 hours following oral administration; (b) a first delayed release dosage unit comprising a second dose of milnacipran resulting in a second plasma level peak at a time of more than 3 hours to

less than 14 hours following oral administration; and optionally (c) a second delayed release dosage unit comprising a third dose of milnacipran resulting in a third plasma level peak at a time between approximately 5 hours to less than 18 hours following oral administration of the formulation; and wherein there is a lag time where there is substantially no release of milnacipran between the release of the immediate release dosage unit and the release of the first delayed release dosage unit. However, the claims are devoid of any structural elements that correlate to the function which is to be achieved with the claimed composition. For example, a variety of oral formulations are known in the art to be capable of producing a pharmaceutical formulation, e.g. liquid, solid, tablet, powder, caplet, etc. Applicant has identified on pages 24-27 of the instant specification several generic types of formulations which may provide pulsatile release. Applicant has demonstrated a limited number of examples of a formulation that demonstrates the claimed properties, e.g. see Examples 5 and 6, describing an enteric coated tablet having specific excipients in particular amounts. Therefore, it is clear that Applicant had possession of such a specific formulation at the time of filing as identified in Examples 5 and 6, but the specification as originally filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed dosage formulation, having an "immediate release dosage unit" and a "first delayed release dosage unit," one would have to determine the type of formulation to be prepared (e.g. liquid, solid, tablet (e.g. compression coated, multilayered, etc.), powder, capsule, etc.), and further which out of an almost unlimited number of excipients available to the skilled artisan should be used

to arrive at a formulation having the claimed functional properties. For example, one would have to determine proper amounts and ratios of structural features, such as active ingredients and excipients, thicknesses of coatings, sizes of particles, etc., each of which would be critical in the resulting functional properties of a formulation. Applicant's limited disclosure of one particular formulation which has the claimed functional properties does not provide support that Applicant envisaged the invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an indication of what the formulation does, rather than what it is. See MPEP 2163 and *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6-10 and 15-17 and 19-21 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137).

Midha discloses that pharmaceutical dosage forms are known which provide a variety of drug release profiles, and that for some drugs it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug, followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily (column 1, lines 18 – 43). The specific example of such a drug which is formulated as a pulsatile release dosage that is taught by Midha is methylphenidate, which may be used in the treatment of attention deficit disorder, narcolepsy, and depression (column 2, lines 5 – 15). Upon administration of the pulsatile release formulation, the first drug release pulse occurs within 1 – 2 hours of ingestion, which is followed by substantially no drug release, after which a second dose is released within 3 – 5 hours of ingestion, followed by a second non-release interval. A third dose occurs from 7 – 9 hours following ingestion (column 4, lines 41+). These dosage units may be in the form of beads or particles which release the drug at different times (column 5, lines 10 – 30), of the delayed release function may be due to the presence of a coating (column 5, lines 35+). Additional

active agents may be formulated to prepare a combination therapy dosage, such as amphetamines, doxapram, fluoxetine, etc. (column 8, lines 42+).

Midha fails to specifically recite that the active agent which is formulated as a pulsatile release dosage is milnacipran.

Ansseau teaches that milnacipran is a pharmaceutical which is used for the treatment of depression. Milnacipran is known to be associated with various side effects, such as nausea, insomnia, vomiting, etc. (Table 4). Studies wherein 200 mg/day of milnacipran (i.e. as 100 mg twice a day) is administered, rather than 100 mg/day once a day, are significantly more effective (page 135 – 136). When administered as a single daily dose in the evening, rather than a divided daily dose, inadequate plasma levels were obtained, likely due to the relatively short half-life of milnacipran, which is about 7 hours, with only an inactive n-dealkylated metabolite (page 136).

Ansseau does not teach a pulsatile release formulation of milnacipran. It would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile-release dosage because Midha teaches that pulsatile release formulations (i.e. of an alternative depression medication), including formulations having a release profile within the claimed range, are useful for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+). One would have been motivated to do so because Ansseau specifically teaches that milnacipran has only a 7 hour plasma elimination half-life, and has previously been administered in two divided daily doses (page 136). One would have had a reasonable expectation of

success in using a 200 mg dosage in the formulation because Ansseau teaches that such dosages were successful in the treatment of depression. With regard to claim limitations such as C_{max} values, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 1-3, 6-12, 15-17 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137), further in view of Pailard (US 6,699,506).

The rejection over Midha in view of Ansseau is applied as above.

Midha and Ansseau do not teach enantiomers of milnacipran.

Paillard teaches a pharmaceutical composition for prolonged release of a single daily dose of 50 to 240 mg of milnacipran (column 1, lines 30 – 35). A racemic mixture or pure enantiomeric form of milnacipran may be administered (column 1, line 65 – column 2, line 3). The formulation comprises a mixture of microparticles that release

the drug at different times (column 1, line 30 – 53), and side effects of the drug are reduced. The microparticles contain a coating such as Eudragit NE30D, RS 100, RL 100, etc. (column 6, lines 45 – 68).

Paillard teaches an extended release, rather than a pulsatile release, formulation of milnacipran.

It would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile-release dosage because Midha teaches that pulsatile release formulations (i.e. of an alternative depression medication), including formulations having a release profile within the claimed range, are useful as an alternative to immediate-release or extended-release formulations for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+). One would have been motivated to do so, and would have had a reasonable expectation of success in doing so, because Ansseau specifically teaches that milnacipran has only a 7 hour plasma elimination half-life, and has previously been administered in two divided daily doses (i.e. 200 mg) (page 136). It would have further been obvious to include an enantiomer of milnacipran in the formulation because Paillard teaches that cis and trans enantiomers may be used in modafinil formulations for the treatment of depression.

Claims 1-3, 6-12, 14-17 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137), further in view of Rao (US 2003/0203055).

The rejection over Midha in view of Ansseau is applied as above.

Midha and Ansseau do not teach para-hydroxy milnacipran.

Rao teaches that the para-hydroxylated derivative of milnacipran is particularly useful, and also teaches that milnacipran can be administered in enantiomerically pure form (e.g., the pure dextrogyral enantiomer) or as a mixture of dextrogyral and levrogyral enantiomers, such as a racemic mixture, may be used (paragraphs 0105-0107). Rao also teaches delayed release formulations, including enteric coatings (paragraph 0205).

It would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile-release dosage because Midha teaches that pulsatile release formulations (i.e. of an alternative depression medication), including formulations having a release profile within the claimed range, are useful as an alternative to immediate-release or extended-release formulations for drugs which have a short half-life and must otherwise be administered two or three times daily (column 1, lines 18+). One would have been motivated to do so, and would have had a reasonable expectation of success in doing so, because Ansseau specifically teaches that milnacipran has only a 7 hour plasma elimination half-life, and has previously been administered in two divided daily doses (i.e. 200 mg) (page 136). It would have further been obvious to include para-hydroxy milnacipran or an enantiomer of milnacipran in

the formulation because Rao teaches such derivatives and enantiomers may be used in modafinil formulations for inhibiting norepiniphrine and serotonin reuptake.

Claims 1-3, 6-10 and 15-17 and 19-21 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476), in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137) and Neliat *et al.* (*Neuropharmacology,* 35, 1996, p. 589-593*)*, further in view of Devane (US 6,228,398).

The rejection over Midha in view of Ansseau is applied as above.

It is noted that Midha discloses a lipopholic drug, methylphenidate, rather than a lipophobic drug, such as milnacipran, as claimed.

Milnacipran is shown to be lipophobic, and to have a relatively short half-life, requiring two daily doses. See Neliat, page 592, left column.

Devane teaches multiparticulate modified release compositions that deliver an active ingredient in a pulsed or bimodal manner. The composition includes an immediate release portion and a controlled release coating (abstract). A lag time is provided between release of the active ingredient from first and second population particles (see column 4, lines 26-45). While a preferred active ingredient is methylphenidate (column 4, line 57), any active ingredient for which it is useful to combine the advantages of a pulsatile release plasma profile with a reduced frequency dosage regime may be used, including drug components acting on the central nervous system (column 6, lines 13+). A drug may be accompanied by, for example an enhancer compound in order to modify the bioavailability or therapeutic effect of the

drug compound. An "enhancer" refers to a compound which is capable of enhancing the absorption and/or bioavailability of an active ingredient by promoting the transport across the GIT in an animal. Enhancers include e.g. medium chain fatty acids, etc. (column 7, lines 4-19).

Therefore, while the lipophilic methylphenidate may exhibit differential absorption properties from lipophobic milnacipran, it would have been well within the skill of the ordinary artisan to include additional components in a formulation, such as an enhancer which may be employed to enhance absorption in the GIT / bioavailability of the drug when the teachings of Midha and Ansseau are taken in view of Devane to arrive at the desired and beneficial release profile as disclosed by Midha for a drug having a short half-life and requiring twice daily dosage, thus improving patient compliance.

Claims 1-3, 6-10 and 15-17 and 19-21 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476), in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137) and Neliat *et al.* (*Neuropharmacology,* 35, 1996, p. 589-593), further in view of Watanabe (US 7,008,640).

The rejection over Midha in view of Ansseau is applied as above.

It is noted that Midha discloses a lipopholic drug, methylphenidate, rather than a lipophobic drug, such as milnacipran, as claimed.

Milnacipran is shown to be lipophobic, and to have a relatively short half-life, requiring two daily doses. See Neliat, page 592, left column.

Watanabe teaches pharmaceutical compositions for oral use with improved absorption comprising a drug, aminoalkyl methacrylate copolymer E and acidic substance (abstract). The small intestine of humans is the longest section of the digestive tract and its effective surface area for absorption is large, therefore it is the ideal site for absorption of drugs. However, absorption is strongly restricted in the case of drugs that are very water soluble (paragraph 0003). Aminoalkyl methacrylate copolymer E can be dissolved of course in the small intestine with a large effective absorption surface area, including the duodenum of the upper small intestine and the jejunum and ileum, etc., as well as in the colon, including the ascending colon, transverse colon, descending colon, and sigmoid colon, and rectum, etc., of the lower digestive tract with a low water content, and as a result, the entire digestive tract becomes the effective absorption site of the drug (paragraph 0074). Examples of drugs that are difficult to absorb due to interaction with the digestive tract mucous layer, etc. may be used, including milnacipran (see paragraph 0075 and 0076, right column). The pharmaceutical composition for oral use of improved absorption can be used in a variety of pharmaceutical including timed-release or pulsed-release pharmaceutical preparations, enteric preparations, colon-released pharmaceuticals, etc. (paragraph 0089).

Therefore, while the lipophilic methylphenidate may exhibit differential absorption properties from lipophobic milnacipran, it would have been well within the skill of the ordinary artisan to include additional components in a formulation, such as an aminoalkyl methacrylate copolymer E, which may be employed to enhance absorption

in the GIT / bioavailability of a hydrophilic drug such as milnacipran, when the teachings of Midha and Ansseau are taken in view of Watanabe, to arrive at the desired and beneficial release profile as disclosed by Midha for a drug having a short half-life and requiring twice daily dosage, thus improving patient compliance.

Response to Arguments

Applicant argues on page 10 of the Response that the prior art teaches away from the claimed invention by disclosing the delivery of lipophilic drugs, such as methylphenidate, in areas of the gastrointestinal tract where drugs that are lipophilic would be expected to be absorbed. Applicant asserts that at the time the invention was made, one of ordinary skill would not have been motivated to release a drug, such as milnaciprin, which is lipophobic, in areas of the gastrointestinal tract where only lipophilic drugs are expected to be absorbed.

Applicant's arguments regarding the prior art's "teaching away" from the claimed invention have been fully considered. However, it is deemed that the Midha reference does not reach the level of a teaching away from preparing a formulation of a lipophobic drug, as suggested by Applicant. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). The

Midha reference merely teaches a pulsatile release formulation of methylphenidate, which happens to be a lipophilic drug. There is no teaching in Midha that suggests that formulation of a lipophilic drug would be unsuccessful, and thus it is considered that the reference does not reach the level of a teaching away from formulation of lipophilic drugs.

Applicant further argues on pages 11-13 of the Response that Midha's pulsatile release delivery of methylphenidate is illustrated as shown in Figure 1. Applicant asserts that under fasted conditions, after two hours a drug dosage would be in the jejunum of the small intestine; after three hours a drug dosage would be in the ileum; after five hours a dosage would be entering the colon; after 7-9 hours the dosage would still be in the colon, and that under fed conditions, the drug would be entering the colon after seven hours. Applicant argues that methylphenidate is lipophilic, and that a person of ordinary skill would have had a reasonable expectation that a lipophilic drug, such as methylphenidate would be entering the colon after five hours post ingestion. Applicant asserts that one would not have a reasonable expectation of success that a drug such as milnacipran which is lipophobic would be colonically absorbed. Applicant cites the Keller declaration, and contends that after 6 to 10 hours, the plasma concentration of milnacipran surprisingly and unexpectedly reaches a maximum level indicating that milnacipran is still being absorbed 6-10 hours post ingestion, and that at this point milnaciprin is in the colon regardless of fed or fasting conditions. Applicant asserts that the results are surprising and unexpected because the skilled artisan would

not have expected a lipophobic drug (a) to be absorbed in the colon and (b) be absorbed in the colon to such a high extent.

This is not found to be persuasive. While the Keller declaration has been fully considered, is insufficient to overcome the rejection of the pending claims based upon the Midha and Ansseau references as set forth in the last Office action because: it refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. For example, the instant claims only require a first delayed pulse resulting in a second plasma level peak at a time of 3 hours to less than 14 hours following oral administration of the formulation. A second delayed release dosage unit is optional and results in a third plasma level peak at a time of 5 hours to less than 18 hours following oral administration of the formulation. Therefore, Applicant's claimed composition does not necessarily require colonic absorption since the only required second, or delayed, pulse may occur as at three hours post administration, at which point the dosage has not reached the colon, according to Applicants Response, pages 11-12.

Conclusion

No claims are allowed at this time. The following references are made of record but are not relied upon for rejection at this time: US 5,158,777; US 6,419,954; US 5,914,134.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS